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Terms	Documents
liposome same skin same (neutral adj1 ph)	0

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L5

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<u>L5</u>	liposome same skin same (neutral adj1 ph)	0	<u>L5</u>
<u>L4</u>	liposom\$ adj5 acidif\$	40	<u>L4</u>
<u>L3</u>	(liposom\$) same (stabili\$ adj10 triethanolamine)	7	<u>L3</u>
<u>L2</u>	(liposom\$) adj10 stabili\$ adj10 triethanolamine	0	<u>L2</u>
<u>L1</u>	(liposom\$) adj5 stabili\$ adj5 triethanolamine	0	<u>L1</u>

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L3: Entry 19 of 31

File: USPT

Sep 19, 2006

DOCUMENT-IDENTIFIER: US 7108863 B2

TITLE: Liposome composition for improved intracellular delivery of a therapeutic agent

PRIOR-PUBLICATION:

DOC-ID

DATE

US 20020192275 A1

December 19, 2002

Description Paragraph (139):

Namalwa cells were maintained in logarithmic growth conditions in RPMI 1640 supplemented with 10% FBS at 37.degree. C. in a humidified atmosphere containing 5% CO.sub.2. Cells (1.0.times.10.sup.8) were collected by centrifugation (1000 rpm for 10 min) and washed with 20 ml of TEA buffer (10 mM triethanolamine, 0.25 M sucrose, 10 mM acetic acid, and 1 mM EDTA, pH 7.4). The washed cells were resuspended in 4 ml TEA buffer and a protease inhibitor cocktail formulated for mammalian cell extracts (4-(2-amino-ethyl)-benzenesulfonyl fluoride, pepstatin A, trans-epoxysuccinyl-L-leucylamino (4-guanidino)butane, bestatin, leupeptin, and aprotinin; Sigma, Mo., USA) was added at 100 .mu.l per gram of cells. The cells were ruptured at 4.degree. C. using 40 firm strokes with a tight-fitting Dounce homogenizer. Unbroken cells were pelleted by centrifugation at 1000 rpm for 10 min at 4.degree. C. The CFE was carefully removed from the cell pellet and then diluted to 6 ml with the addition of TEA buffer. The CFE was adjusted to pH 5.5, approximating the lysosomal pH of between 5 and 6.5 (Tycko, B. et al., Cell, 28:643 (1982); Tycko, B. et al., J. Cell Biol., 97:1762 (1983)).

Description Paragraph (154):

For each time point, three aliquots of the nuclear fractions (0.2 ml each) were placed in 1.3 ml TEA. DNA was enzymatically digested by the addition of 10 .mu.l digitonin solution (25 mg/ml in sterile PBS, Sigma, St. Louis, Mo.), 10 .mu.l MgCl.sub.2 solution (57 mg/ml in sterile PBS) and 50 .mu.l DNase 1 solution (3 mg/ml in sterile PBS, Sigma). Following digestion at 22.degree. C. for 2 hours, the doxorubicin fluorescence was recorded (excitation at 480 nm and emission at 595 nm). The purity of the nuclear fraction was checked by determining the levels of enzyme markers for various cellular organelles (Lopes de Menezes et al., J. Liposome Res., 9:199 (1999)).

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L3: Entry 18 of 31

File: PGPB

Aug 1, 2002

DOCUMENT-IDENTIFIER: US 20020102295 A1

TITLE: Compositions for application to the skin or hair

Summary of Invention Paragraph:

[0078] Examples of suitable soaps include, but are not limited to, fatty acids reacted with potassium, sodium, ammonium, lithium, triethanol amine bases to form soaps such as sodium cocoate or triethanolamine cocoate.

Detail Description Paragraph:

[0120] The Deionized water was added in a suitable container. The Salcare SC96 was then added and mixed for approximately 10 minutes or until the mixture was free of lumps. The mixture was then heated to 60.degree. C. The phenyl trimethicone liposomes and PVP liposomes were then added and mixed at 500 rpm for 10 minutes. The phenyl trimethicone, glycerin, panthenol, triethanolamine and phenonip were then added and mixed while being cooled to 35.degree. C. At 35.degree. C. the fragrance was then added and mixed for 5 minutes. The composition was then cooled down to room temperature.

Detail Description Table CWU:

4TABLE 4 Liposomal PVP and liposomal Phenyl Trimethicone conditioner for increasing shine of hair Range Component (% W/W) Tradename Supplier DI Water 40-99.9 -- -- Phenyl Trimethicone 0.01-10 DC 556 Dow Corning Phenyl Trimethicone 0.001-95 -- Example 1 Liposomes Formula 2 Glycerin 0-60 Glycerine Condor Corp Polyquaternium-37 0.01-10 Salcare Ciba Propylene Glycol SC96 Dicaprylate/Dicaprate PPG-1 Trideceth-6 Panthenol 0.01-5 Panthenol Hoffman La -50 Roche PVP Liposomes 0.001-95 -- Example 1 (table 1) Formula 1 Phenoxyethanol 0.01-5 Phenonip Nipa Hardwick Methylparaben Ethylparaben Propylparaben Butylparaben Isobutylparaben Triethanolamine 0.001-2 TEA 99% Van Waters & Fragrance 0.001-2 Fragrance Givaudan Roure

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L3: Entry 16 of 31

File: PGPB

May 15, 2003

DOCUMENT-IDENTIFIER: US 20030091621 A1

TITLE: Liposome loading with metal ions

Brief Description of Drawings Paragraph:

[0041] FIG. 1A: A graph showing loading of irinotecan into DSPC/DSPG (80:20 mole ratio) liposomes as a function of time using 100 mM Cu(II)gluconate buffered to pH 7.4 with triethanolamine (TEA) as the internal medium and 300 mM sucrose, 20 mM HEPES, 30 mM EDTA (SHE), pH 7.4 as the external medium. Loading was carried out at 50.degree. C. at a drug-to-lipid mole ratio of 0.1:1.

Brief Description of Drawings Paragraph:

[0042] FIG. 1B: A graph showing loading of daunorubicin into DSPC/DSPG (90:10 mole ratio) liposomes as a function of time using 150 mM CuSO.sub.4, 20 mM histidine adjusted to pH 7.4 with TEA as the internal medium and SHE, pH 7.4 as the external medium. Loading was carried out at 60.degree. C. at a drug-to-lipid weight ratio of 0.1:1.

Brief Description of Drawings Paragraph:

[0043] FIG. 2: A graph showing loading of irinotecan into DPPC/Chol (55:45 mole ratio) liposomes as a function of time using 100 mM Cu(II)gluconate adjusted to pH 7.4 with TEA as the internal medium and SHE, pH 7.4 as the external medium. Loading was carried out at 50.degree. C. at a drug-to-lipid weight ratio of 0.1:1.

Brief Description of Drawings Paragraph:

[0045] FIG. 4A: A graph showing loading of irinotecan into floxuridine (FUDR) containing DSPC/DSPG liposomes at an 85:15 mole ratio as a function of time using 100 mM Cu(II)gluconate, 220 mM TEA, pH 7.4 as the internal medium and 300 mM sucrose, 20 mM HEPES, pH 7.4 as the external solution. FUDR was passively encapsulated and irinotecan loading was carried out at 50.degree. C. at a drug-to-lipid mole ratio of 0.1:1.

Brief Description of Drawings Paragraph:

[0046] FIG. 4B: A graph showing loading of irinotecan into FUDR-containing DSPC/Chol/DSPG (70:10:20 mole ratio) liposomes as a function of time using 100 mM Cu(II)gluconate, 220 mM TEA, pH 7.4 as the internal medium and either 20 mM HEPES, 150 mM NaCl (HBS), pH 7.4 (.circle-solid.) or 300 mM sucrose, 20 mM HEPES, pH 7.4 (.smallcircle.) as the external buffer. FUDR was passively encapsulated and irinotecan loading was carried out at 50.degree. C. at a drug-to-lipid mole ratio of 0.1:1.

Brief Description of Drawings Paragraph:

[0047] FIG. 5: A graph showing loading of irinotecan into carboplatin-containing DSPC/DSPG (80:20 mole ratio) liposomes as a function of time using 150 mM CuSO.sub.4 adjusted to pH 7.4 with TEA as the internal medium and SHE, pH 7.4 as the external buffer. Carboplatin was passively encapsulated and irinotecan loading was carried out at 60.degree. C. at a drug-to-lipid weight ratio of 0.1:1.

Detail Description Paragraph:

[0153] Preferred metal compatible solutions are those that are also pharmaceutically acceptable such as ones comprising triethanolamine (TEA), sodium

chloride, sodium acetate/acetic acid, sodium citrate/citric acid or sugars such as sucrose, dextrose and lactose. Phosphate and carbonate based solutions (although pharmaceutically acceptable) will have limited use except at pH's outside of normal physiological ranges, due to the likelihood of metal precipitation. Preferably, the metal compatible solution is buffered and has pH in a physiological range.

Detail Description Paragraph:

[0168] The following examples are given for the purpose of illustration and are not by way of limitation on the scope of the invention. Unless otherwise specified, pH was adjusted using triethanolamine (TEA) and results shown in the drawings are from a single representative example.

Detail Description Paragraph:

[0174] In order to determine whether copper loading of irinotecan in the absence of a pH gradient could occur using a cholesterol-free formulation, DSPC/DSPG (80:20 mole ratio) liposomes containing copper(II)gluconate were prepared with an external and internal pH of 7.4. Lipid films of DSPC/DSPG at a mole ratio of 80:20 were prepared as described above in the method section. The lipid films were hydrated in 100 mM Cu(II)gluconate adjusted to pH 7.4 with triethanolamine (TEA) and extruded at 70.degree. C. The liposomes were buffer exchanged into 300 mM sucrose, 20 mM HEPES, 30 mM EDTA (SHE buffer), pH 7.4 by tangential flow dialysis and subsequently washed three times in 6 mL of SHE, pH 7.4 to remove any copper(II)gluconate from the extraliposomal solution. Irinotecan was added to the liposome preparation at a 0.1:1 drug-to-lipid mole ratio and incubated at 50.degree. C. The extent of drug loading was determined as described in the methods by measuring absorbance at 370 nm and lipid levels were determined by liquid scintillation counting.

Detail Description Paragraph:

[0176] Loading of daunorubicin into DSPC/DSPG (90:10 mole ratio) liposomes containing encapsulated CuSO₄ buffered to pH 7.4 was also investigated. Lipid films were prepared according to the methods except DSPG was dissolved in chloroform/methanol/water (50:10:1 v/v). A solution of 150 mM CuSO₄, 20 mM histidine (adjusted to pH 7.4 using TEA), was employed as the hydration medium and MLVs were extruded at 70.degree. C. The liposomes were exchanged into SHE, pH 7.4 using a hand-held tangential flow dialysis column. Daunorubicin was loaded at a 0.1:1 drug/lipid weight ratio. A drug-to-lipid ratio at various time points during loading was determined by measuring absorbance at 480 nm after solubilization in detergent to quantify daunorubicin as described; lipid levels were determined by liquid scintillation counting.

Detail Description Paragraph:

[0178] Copper loading of irinotecan into cholesterol-containing liposomes exhibiting no pH gradient was investigated employing DPPC/Chol (55:45 mole ratio) liposomes. The liposomes were prepared as described in the methods by hydrating lipid films in a solution of 100 mM copper(II)gluconate adjusted to pH 7.4 with TEA. Liposomes were extruded at 65.degree. C. and the external buffer of the liposomes was exchanged to SHE, pH 7.4 by tangential flow dialysis. Liposomes were incubated with irinotecan at a 0.1:1 drug-to-lipid weight ratio at 50.degree. C. and the extent of drug loading was determined as described by measuring absorbance at 370 nm after solubilization by detergent.

Detail Description Paragraph:

[0184] DSPC/DSPG (85:15 mole ratio) liposomes containing FUDR were prepared by dissolving DSPC in chloroform and DSPG in chloroform/methanol/water (50:10:1 v/v). The lipids were then combined together at an 85:15 mole ratio and labeled with trace amounts of 14C-CHE. The samples were hydrated in 100 mM copper(II)gluconate, 220 mM TEA, pH 7.4, containing 24.62 mg/mL (100 mM) FUDR with trace levels of 3H-FUDR at 70.degree. C. The resulting MLVs were extruded at 70.degree. C., then buffer exchanged first into saline and next into SHE, pH 7.4 using a hand-held tangential flow dialysis column. This sample was then exchanged into 300 mM

sucrose, 20 mM HEPES, pH 7.4 to remove any EDTA in the exterior buffer.

Detail Description Paragraph:

[0190] Loading of irinotecan into DSPC/DSPG (80:20 mole ratio) liposomes with passively encapsulated carboplatin was measured using liposomes prepared as described above except that lipid films were hydrated in 150 mM CUSO.sub.4 (adjusted to pH 7.4 using TEA), containing 25 mg/ml carboplatin. Samples were extruded and external buffers exchanged into SHE, pH 7.4, using a hand-held tangential flow dialysis column. Irinotecan was added at 60.degree. C. at a drug-to-lipid weight ratio of 0.1:1 and uptake was measured as previously described. Atomic absorption spectrometry (AA) was used to determine carboplatin concentrations and absorbance at 370 nm was measured to determine irinotecan concentrations. The initial carboplatin drug-to-lipid weight ratio was 0.030, and 0.025 after loading of irinotecan occurred.

Detail Description Paragraph:

[0195] Solutions of cobalt, nickel, manganese, cadmium, zinc and copper were prepared at concentrations of 150 and 300 mM in 20 mM histidine. Triethanolamine (1.13 g/mL) was added drop-wise until the resulting solution was pH 7.4 or until the solution was cloudy in appearance (over a 10 minute observation period). Typically, less than 500 (L of 1.13 g/mL triethanolamine was added. Subsequent to addition of triethanolamine, the solutions were visually inspected to determine whether precipitation of the metal had occurred. A cloudy appearance of the solution indicated the presence of a precipitate whereas clarity of the solution indicated a lack of precipitation. The results are shown in Table 2.

Detail Description Paragraph:

[0238] Liposomes composed of DSPC/DSPG (80:20 mole ratio) were prepared following the procedures as described in Example 1. DSPC and DSPG lipids were dissolved in chloroform and chloroform/methanol/water (50:10:1 v/v), respectively. The lipids were then combined in appropriate amounts for each formulation. Solvent was removed under a steady stream of N.sub.2 gas while maintaining the temperature at 70.degree. C. and put under vacuum for 5 minutes. The resulting lipid films were redissolved in chloroform to further remove any methanol or water and then solvent was removed as before and dried under vacuum to remove any residual solvent. The samples were subsequently rehydrated in 150 mM CUSO.sub.4, pH 7.4 (pH adjusted with TEA) and the resulting MLVs were extruded at 70.degree. C. Liposome samples were either run down a 15 mL Chelex-100.TM. (BioRad) column equilibrated with 150 mM NaCl at 0.5 mL/min or buffer exchanged into saline and further exchanged into 300 mM sucrose, 20 mM HEPES, pH 7.4 using tangential flow. Liposomes that were passed through the Chelex-100.TM. column were subsequently exchanged into 300 mM sucrose, 20 mM HEPES, pH 7.4 using tangential flow.

Detail Description Table CWU:

2TABLE 2 Metal Concentration (mM) Sulfate Chloride Nitrate Cobalt 300 no ppt no ppt -- 150 no ppt no ppt -- Nickel 300 no ppt no ppt -- 150 no ppt no ppt -- Manganese 300 no ppt ppt -- 150 no ppt ppt -- Cadmium 300 no ppt ppt -- 150 no ppt ppt -- Zinc 300 ppt ppt -- 150 ppt ppt -- Copper 300 no ppt no ppt no ppt 150 no ppt no ppt -- ppt: represents that the formation of a precipitate occurred after the addition of triethanolamine within a time course of 10 minutes no ppt: represents that the formation of a precipitate did not occur after addition of triethanolamine to achieve a pH of 7.4 and within a time course of 10 minutes. dashed line: not measured Concentrations of the indicated metal are concentrations before addition of triethanolamine.

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DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR

<u>L3</u>	L2 and triethanolamine
<u>L2</u>	liposome same tea
<u>L1</u>	ethasome same tea

31	<u>L3</u>
98	<u>L2</u>
0	<u>L1</u>

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liposome same (\$terpen\$ adj5 hydroxide or triethanolamine)	192

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L18 and (citr\$ or acidif\$)

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DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR

<u>L18</u>	liposome same (\$terpen\$ adj5 hydroxide or triethanolamine)	192	<u>L18</u>
<u>L17</u>	L16 and 424/450.ccls.	253	<u>L17</u>
<u>L16</u>	L15 and (ethanol or alcohol)	414	<u>L16</u>
<u>L15</u>	liposome same (load\$) same ph	563	<u>L15</u>
<u>L14</u>	liposome same (triethanolamine) same (acidif\$)	0	<u>L14</u>
<u>L13</u>	liposome same (triethanolamine) same (citric or citrate)	13	<u>L13</u>
<u>L12</u>	L11 and base	24	<u>L12</u>
<u>L11</u>	L9 and acid	31	<u>L11</u>
<u>L10</u>	L9 and \$terpen\$	2	<u>L10</u>
<u>L9</u>	L8 and 424/450.ccls.	32	<u>L9</u>
<u>L8</u>	liposome same \$solvent same (propylene adj1 glycol)	1065	<u>L8</u>
<u>L7</u>	L6 and 424/450.ccls.	11	<u>L7</u>
<u>L6</u>	liposome same (butylene adj1 glycol)	103	<u>L6</u>
<u>L5</u>	(liposome) same (glycol or glycerol) and (alcohol adj3 inject\$)	19	<u>L5</u>

<u>L4</u>	(liposome) adj10 (glycol or glycerol) and (alcohol adj3 inject\$)	0	<u>L4</u>
<u>L3</u>	(glycol) adj5 (ursolic or oleanolic or betulinic or \$boswellic)	0	<u>L3</u>
<u>L2</u>	L1 and (ursolic or oleanolic or betulinic or \$boswellic)	36	<u>L2</u>
<u>L1</u>	liposome adj10 (glycol or glycerol)	2691	<u>L1</u>

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L7: Entry 11 of 11

File: USPT

Oct 6, 1992

DOCUMENT-IDENTIFIER: US 5153000 A

TITLE: Phosphate, liposome comprising the phosphate as membrane constituent, and cosmetic and liposome preparation comprising the liposome

Detailed Description Text (35):

The transparent gel-like cosmetic composition can be prepared by mixing the phosphates (a), water, and other components. When the liposome comprising the phosphate (a) of the present invention is to be formed in a cosmetic composition, components (b), i.e. the water-soluble base, the surface-active agent, or both, must be included. The liposome-containing cosmetic composition can be prepared according to the above-mentioned method for the preparation of the liposomes. Various active components can be added to the cosmetic composition. These active components may be present in the cosmetic composition as they are incorporated in the liposomes. The following compounds are given as examples of such active components. Vitamins and their derivatives such as vitamin A, vitamin B's, vitamin C, vitamin D, vitamin E, vitamin K, and the like; glycerol and their derivatives such as diglycerol, triglycerol, polyglycerols, monoglycerides, diglycerides, triglycerides, and the like; polyhydric alcohols such as 1,3-butylene glycol, propylene glycol, dipropylene glycol, polyethylene glycol, and the like; sugars and their derivatives such as glucose, fructose, sorbitol, galactose, mannose, inositol, maltitol, maltose, lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides and their derivatives such as hyaluronic acid, chondroitin sulfuric acid, and the like; sugar phosphates and salts thereof as well as their derivatives such as glucose-1-phosphate, glucose-6-phosphate, mannose-6-phosphate, galactose-6-phosphate, fructose-6-phosphate, glucose-1,6-diphosphate, fructose-1,6-diphosphate, fructose-2,6-diphosphate, and their sodium or potassium salts, and the like; amino acid and their derivatives such as alanine, leucine, lysine, asparagine, aspartic acid, cysteine, proline, glutamine, serine, glutamic acid, glycine, histidine, tyrosine, isoleucine, valine, and the like; cholesterol and their derivatives, ceramides and their derivatives, compounds analogous to ceramides, highly unsaturated fatty acids and their derivatives such as linoleic acid, linolenic acid, arachidonic acid, docosahexanoic acid, prostaglandin, prostacyclin, leukotriene, and the like; pyrrolidonecarboxylic acid, glycyrrhizin, bisabolol, benzalconium chloride, benzethonium chloride, menthol, resorcinol hinokitiol, and the like.

Detailed Description Text (102):

Sodium sulfate was dissolved into purified water. To the solution glycerol was added to dissolve. This solution was added to white precipitates of the organic phosphate and the mixture was heated over a water bath at a temperature of about 50.degree. C. with stirring to produce a liposome phase. Separately, a water phase was prepared by adding and dissolving 1,3-butylene glycol and polyethylene glycol 1500 into purified water at room temperature. A solution prepared by adding and dissolving the surface active agent, antiseptic, and perfume into ethanol was added to the water phase and dissolved. To this the liposome phase was added and the mixture was filtered to prepare a lotion.

Current US Original Classification (1):

424/450

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L7: Entry 10 of 11

File: USPT

Dec 17, 1996

DOCUMENT-IDENTIFIER: US 5585109 A

TITLE: Cosmetic delivery system for salicylic acid and process for preparation of same

Detailed Description Paragraph Table (4):

Ingredient	Parts by Weight	Example 4 (Moisturing Liposome Gel) Phase
Lecithin	2.0 1	(a) Preproduct 1
NaPCA	1.0 1	
Glycine	1.0 1	
Trehalose	1.0 1	
Water	86.6 2	
Salicylic Acid	2.0 2	(b) Final Product 4
Chlorphenesin	2.5 3	
Arginine	0.5	
Butylene glycol	3.1	
Carbomer 941	0.3	

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L7: Entry 9 of 11

File: USPT

Apr 6, 1999

DOCUMENT-IDENTIFIER: US 5891465 A

TITLE: Delivery of biologically active material in a liposomal formulation for administration into the mouth

Current US Original Classification (1):

424/450

CLAIMS:

1. A liposomal composition suitable for the aerosol or spray delivery of melatonin to a subject, said composition comprising melatonin and optionally an additional supplement in phospholipid liposomes and a carrier wherein the liposomes have between about 20 nm and 10 microns in diameter and results in absorption into the blood stream, when administered, wherein the phospholipid liposome comprises one or more bilayer forming lipids, wherein said composition provides an increase in bioavailability of said supplement or drug of approximately 20 % or more when compared to an orally administered solid form, and wherein said composition comprises by weight percent, from about 0.25 to 20% lecithin, from about 0.025 to 2% cholesterol or zoosterol or phytosterol, from about 0.01 to 3% antioxidant, from about 0.05 to 0.4% melatonin, from about 0.1 to 20% glycerin, propylene glycol or butylene glycol, from about 0.1% to 10% ethanol, from about 0.015 to 4% anti microbial agent and from about 2 to 99.9% water.

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L7: Entry 8 of 11

File: USPT

Feb 6, 2001

DOCUMENT-IDENTIFIER: US 6183774 B1

TITLE: Stabilizing vitamin A derivatives by encapsulation in lipid vesicles formed with alkylammonium fatty acid salts

Detailed Description Text (14):

In a further embodiment, a co-solvent may also be incorporated with the liposomes of the invention. The co-solvent is not required in the liposome formulations of the invention. Such incorporation may be carried out either prior to or following liposome formulation by incorporating the co-solvent either into the liposome formulation mixture or into the liposome formulation after the liposomes have been made. Examples of such co-solvents to be incorporated include but are not limited to propylene glycol, polyethylene glycol butylene glycol or any combination thereof. Examples of preferred polyethylene glycols include PEG 200, PEG 2000, PEG-4 and PEG-8. The co-solvent to be used in the compositions of the invention are incorporated into the liposome formulation mixture or into the liposome formulation in a concentration range of from about 0% w/w to about 50% w/w. A preferred concentration range for the co-solvent is from about 0% w/w to about 10% w/w.

Current US Original Classification (1):

424/450

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L7: Entry 7 of 11

File: USPT

Dec 30, 2003

DOCUMENT-IDENTIFIER: US 6669932 B2

TITLE: Skin-whitening cosmetic

Detailed Description Text (19):

The liposomal dispersion thus prepared is, if desired, passed through a filter to dress the liposomes. Also if desired, any of polymer substances such as carboxyvinyl polymer, carboxymethyl cellulose, hydroxyethyl cellulose, xanthane gum, poly(oxyethylene)-poly(oxypropylene) block copolymer, etc.; pH-adjusting agents such as citric acid, salts of citric acid, phosphoric acid, salts of phosphoric acid, triethanolamine, potassium hydroxide, sodium hydroxide, lactic acid, salts of lactic acid, etc.; polyhydric alcohols such as glycerin, propylene glycol, butylene glycol, etc.; polysaccharides such as salts of alginic acid, esters of alginic acid, etc.; saccharides such as trehalose, glucose, sorbitol, sucrose, etc.; and cholesterol may be added to the liposomal dispersion in order to improve the stability of the dispersion.

Detailed Description Text (25):

The liposomal composite dispersion thus prepared according to any of the methods (B) (1) to (3) is, if desired, passed through a filter to dress the liposomes. Also, if desired, any of polymer substances such as carboxyvinyl polymer, carboxymethyl cellulose, hydroxyethyl cellulose, xanthane gum, poly(oxyethylene)-poly(oxypropylene) block copolymer, etc.; pH-adjusting agents such as citric acid, salts of citric acid, phosphoric acid, salts of phosphoric acid, triethanolamine, potassium hydroxide, sodium hydroxide, lactic acid, salts of lactic acid, etc.; polyhydric alcohols such as glycerin, propylene glycol, butylene glycol, etc.; polysaccharides such as salts of alginic acid, esters of alginic acid, etc.; saccharides such as trehalose, glucose, sorbitol, sucrose, etc.; and cholesterol may be added to the liposomal dispersion in order to improve the stability of the dispersion. The ratio of the unsaturated fatty acid or its salt or ester to the phospholipid to form liposomes is preferably from 1/5 to 2/1 by mol, more preferably from 1/2 to 3/2 by mol, as the liposomes comprising them in the ratio falling within the defined range produce a higher skin-whitening effect.

Detailed Description Text (41):

Lecithin or hydrogenated lecithin, the unsaturated fatty acid indicated, and vitamin E were dissolved in a solvent such as methylene chloride, and homogenized. Then, purified water was added to the resulting homogenate, from which the solvent had been removed, and mixed by stirring them. The resulting mixture was processed in a French press to form liposomes. The liposomes were added to a solution of collagen and sodium chondroitin sulfate in purified water. The resulting mixture was added to a solution of 1,3-butylene glycol, carboxyvinyl polymer, potassium hydroxide and methyl para-hydroxybenzoate in purified water, and mixed by stirring them. Thus were prepared essence samples.

Detailed Description Text (87):

The phases (A) and (B) were separately dissolved under heat to give uniform mixtures. Then, the phase (B) was added to the phase (A) and mixed by stirring them to give a uniform mixture. The ingredients, egg yolk lecithin, linoleic acid monoglyceride and vitamin E were homogenized, and then hydrated with an aqueous solution (pH 6) containing sodium hydroxide and 1,3-butylene glycol to form

liposomes (of the phase (C)). The resulting phase (C) was mixed with the phase (D), and added to and mixed with the phase (B) by stirring them while the phase (B) was cooled. Thus was prepared a cream mask (pH 6.8).

Current US Cross Reference Classification (2):
424/450

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L9: Entry 30 of 32

File: USPT

Oct 1, 1991

DOCUMENT-IDENTIFIER: US 5053217 A

TITLE: Composition and method

Brief Summary Text (30):

The aerosol compositions of this invention generally contain from 5% to 40%, preferably 10% to 20%, of membrane lipid component a); up to 40%, preferably up to 10%, of water component c); balance ethanol or other water-miscible solvent, all percentages being by weight on the combined weights of components a), b) and c). Water is not critical to promote liposome formation as the pro-liposome is discharged as fine droplets, but may be useful when a water-soluble biologically active material is to be included. When ethanol is used as component b), a minor proportion of propylene glycol or glycerol may be included to reduce possible volatility problems which might arise on spraying. Indeed, propylene glycol or glycerol may be used in partial or complete replacement for ethanol. The proportion by weight of membrane lipid component a) to water miscible solvent component b) is preferably from 1:2 to 1:10.

Current US Cross Reference Classification (3):

424/450

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L9: Entry 29 of 32

File: USPT

Dec 19, 1995

DOCUMENT-IDENTIFIER: US 5476853 A

TITLE: Agent for use as an anti-irritant

Brief Summary Text (16):

Other particular compositions are those wherein the compound (I) is formulated in liposome-containing compositions. Different types of liposomes may be employed such as coarse (multilayer) liposomes or unilamellar liposomes and the like, which are formed, for example, with phosphatidyl cholines, ethanolamines, serines, sphingomyelins, cardiolipins, plasmalogens, phosphatidic acids, cerebrosides and the like. The viscosity of the liposomes can be increased by addition of one or more thickening agents such as xanthan gum, hydroxypropyl cellulose, hydroxypropyl methyl cellulose and mixtures thereof. The aqueous component may consist of water optionally in admixture with electrolytes, buffers and other ingredients such as preservatives. Preferred electrolytes are calcium, sodium and potassium chloride. The organic component may consist of a solvent such as ethanol, glycerol, propylene glycol, a polyethylene glycol and a suitable phospholipid such as, lecithin, phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine, phosphatidyl inositol, lysophosphatidyl choline, phosphatidyl glycerol and the like. Other lipophilic additives which may be added to selectively modify the characteristics of the liposomes are, e.g. stearylamine, phosphatidic acid, tocopherol, cholesterol, lanolin and the like.

Current US Cross Reference Classification (1):

424/450

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L9: Entry 26 of 32

File: USPT

Mar 18, 1997

DOCUMENT-IDENTIFIER: US 5612347 A

TITLE: Agents for preserving or restoring the soundness of the skin

Brief Summary Text (32):

The organic component consists of a suitable non-toxic, pharmaceutically acceptable solvent such as, for example ethanol, glycerol, propylene glycol and polyethylene glycol, and a suitable phospholipid which is soluble in the solvent. Suitable phospholipids which can be employed include lecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, lysophosphatidylcholine and phosphatidyl glycerol, for example. Other lipophilic additives may be employed in order to selectively modify the characteristics of the liposomes. Examples of such other additives include stearylamine, phosphatidic acid, tocopherol, cholesterol and lanolin extracts.

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L10: Entry 2 of 2

File: USPT

Feb 10, 1998

DOCUMENT-IDENTIFIER: US 5716638 A

TITLE: Composition for applying active substances to or through the skin

Brief Summary Text (13):

An important characteristic of ethosomes is enhanced membrane permeability for various compounds. Ethosomal systems, vesicular in nature, depending on the ratio of the components and the chemical structure of the phospholipids, can be comprised of very small entities (nm's) up to larger vesicles (mm's) (see Tables 3-5). High alcoholic (organic solvent) concentration favors the production of ethosomes in nm's range while high aqueous and phospholipid concentrations favor the formation of large size ethosomes. As examples, formulation 509 (Table 4) containing 60% organic solvent and 38% water has a mean population of tens of nm's, while formulation 510 containing 50% organic solvent and 48% water has a mean population of 1 mm. In system 509 the concentration of ethanol was 48% while in formulation 510 the ethanol concentration is only 20%. showing that the alcohol concentration is of great importance in determining vesicle size. The phospholipids which can be used are: phosphatidylcholine (PC), phosphatidylserine (PS), phosphatidic acid (PA), phosphatidylethanolamine (PE), phosphatidylglycol (PPG), hydrogenated PC and others. Some preferred phospholipids are soya phospholipids such as Phospholipon 90 (PL-90). The concentration of phospholipid ranges between about 0.5-10% w/w. Cholesterol at concentrations ranging between about 0.1-1% can also be added to the preparation. Examples of alcohols which can be used are: ethanol and isopropyl alcohol. Examples of glycols are propylene glycol and Transcutol.RTM.. The source of the phospholipids can be egg, soybean, semi-synthetics, and synthetics. Non ionic surfactants can be combined with the phospholipids in these preparations e.g. PEG-alkyl ethers (Brij-52). Cationic lipids like cocoamide, Pae alkyl amines, dodecylamine, cetrimide, and like. The concentration of alcohol (EtOH etc.) in the final product ranges from about 20-50%. The concentration of the non-aqueous phase (alcohol and glycol combination) may range between about 22 to 70%. The rest of the carrier contains water and possible additives. Vesicle formation is dependent on the water: alcohol ratio. This ratio is kept constant in the product, therefore, no changes in the entities population occur. Nevertheless, penetration and evaporation of the alcohol following application to the skin allows the transition from small vesicles to a larger ones, finally resulting in film formation. In contrast to the present state of the art where "tough" liposomes accomplished by addition of different substances like cholesterol to the phospholipids and in absence of alcohol, this invention relates to "soft" vesicles, that can be easily formed in a hydroalcoholic medium. One of the important properties of these systems is that small entities can penetrate into the skin, while larger vesicles can form a reservoir in the skin and a film on the skin surface as a result of solvent evaporation taking place after the application. These carriers can be used to deliver various active agents such as: peptides, anti-aging, tanning agents, vitamins, antiviral drugs, psoriasis treatment agents, melanin, melatonin, hormones, medicinally active components of plants such as oleoresins, volatile oils, glycosides, alkaloides, terpenes and others.

Current US Original Classification (1):

424/450

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L19: Entry 46 of 120

File: PGPB

Jul 10, 2003

DOCUMENT-IDENTIFIER: US 20030129224 A1

TITLE: Lipid carrier compositions and methods for improved drug retention

Summary of Invention Paragraph:

[0007] An advancement in liposome loading techniques was the discovery that an ion gradient can be generated across a liposome membrane in order to actively load an ionizable drug (U.S. Pat. Nos. 5,736,155; 5,077,056; and 5,762,957). This method involves establishing a pH gradient across a liposome bilayer such that an ionizable drug to be encapsulated within a liposome is uncharged in the external buffer and charged within the aqueous interior. This allows the drug to readily cross the liposomal bilayer in the neutral form and to be trapped within the aqueous interior of the liposome due to conversion to the charged form. The most common method of loading agents with ionizable amine groups employs an internal buffer composition such as citrate, pH 4.0 and a neutral exterior buffer; however, other methods of establishing a pH gradient have also been used. Generally, the internal buffer concentrations employed for loading of drug are between 300 and 600 mM; although concentrations as low as 100 mM have been reported (U.S. Pat. No. 5,762,957).

Brief Description of Drawings Paragraph:

[0024] FIG. 1: A graph showing the percent initial vincristine-to-lipid weight ratio (initial drug-to-lipid weight ratio was 0.1:1) in the blood after intravenous injection of Balb/c mice at various time points for liposomes consisting of DSPC/DSPE-PEG2000 (95:5 mole ratio) utilizing 300 mM citrate (filled circles) and 150 mM (open circles) as the internal loading buffer (about 600 and 300 mOsm/kg, respectively) and liposomes consisting of DSPC/cholesterol (55:45 mole ratio) utilizing 300 mM citrate (filled triangles) and 150 mM citrate (open triangles) as the internal loading buffer.

Brief Description of Drawings Paragraph:

[0025] FIG. 2: A graph showing the percent initial ratio of daunorubicin-to-lipid (initial drug-to-lipid mole ratio was 0.2:1) remaining in the blood after intravenous injection of Balb/c mice as a function of time for liposomes consisting of DSPC/cholesterol (55:45 mole ratio, filled circles), DSPC/cholesterol/DSPE-PEG2000 (50:45:5 mole ratio, open circles) and DSPC/DSPE-PEG2000 (95:5 mole ratio), utilizing either 150 (filled triangles) or 300 mM (open triangles) citrate, pH 4 (300 or 600 mOsm/kg, respectively) as the internal buffer.

Brief Description of Drawings Paragraph:

[0026] FIG. 3A: A histogram showing the percent initial daunorubicin-to-lipid ratio (initial drug-to-lipid mole ratio was 0.2:1) remaining in the blood 4 hours after intravenous injection of Balb/c mice with liposomes consisting of DSPC/DSPE-PEG2000 (95:5 mole ratio) utilizing 100 mM, 150 mM, 200 mM, 250 mM and 300 mM citrate (200, 300, 400, 500 and 600 mOsm/kg, respectively), pH 4.0 as the internal loading buffer.

Brief Description of Drawings Paragraph:

[0027] FIG. 3B: A graph showing idarubicin-to-lipid mole ratio in the blood after intravenous injection of Balb/c mice at various time points for liposomes consisting of DSPC/DSPE-PEG2000 (95:5 mole ratio) utilizing 100 mM (filled

triangles), 150 mM (open circles) and 300 mM (filled circles) citrate, pH 4 (200, 300 and 600 mOsm/kg, respectively) as the internal loading buffer.

Detail Description Paragraph:

[0067] Where the pH gradient loadable drug is one that loads in response to a transmembrane pH gradient where the interior of the liposome is relatively acidic with respect to the exterior, acidic internal loading buffers may be used. The acidic loading buffers, which in general can be used in practicing this invention include organic acids, e.g., monofunctional pyranosidyl acids such as glucuronic acid, gulonic acid, gluconic acid, galacturonic acid, glucoheptonic acid, lactobionic acid, and the like, alpha-hydroxy polycarboxylic acids such as citric acid, iso-citric acid, hyaluronic acid, carboxypolymethylenes, and the like, amino acids such as aspartic acid, carboxyaspartic acid, carboxyglutamic acid, and the like, saturated and unsaturated, unsubstituted and substituted aliphatic dicarboxylic acids such as succinic acid, glutaric acid, ketoglutaric acid, tartaric acid, galactaric acid, maleic acid, fumaric acid, glucaric acid, malonic acid, and the like, phosphorus-containing organic acids such as phytic acid, glucose phosphate, ribose phosphate, and the like, and inorganic acids, e.g., sulfonic acid, sulfuric acid, phosphoric acid, polyphosphoric acids, and the like. Such buffers are best used at pH of about 2.0 to 4.5. Preferably, the interior buffer is an .alpha.-hydroxy polycarboxylic acid such as citric acid. The exterior buffer may be a buffer present at neutral pH such as HEPES, pH 7.0. Most preferably, the internal buffer is citrate, pH 2.0 to 4.0. The internal buffer osmolarity of the liposome is less than 500 mOsm/kg, preferably less than 300 mOsm/kg.

Detail Description Paragraph:

[0079] Preferably, the pharmaceutical compositions are administered intravenously. Typically, the formulations will comprise a solution of the liposomes suspended in an acceptable carrier, preferably an aqueous carrier. A variety of aqueous carriers may be used, e.g., water, buffered water, 0.9% isotonic saline, 5% dextrose and the like. These compositions may be sterilized by conventional, well known sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous solution prior to administration. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions, such as pH adjusting and buffering agents, tonicity adjusting agents, wetting agents and the like, for example, sodium acetate, sodium lactate, sodium chloride, potassium chloride, calcium chloride, sorbitan monolaurate, triethanolamine oleate, etc.

Detail Description Paragraph:

[0084] Solutions of lipids in chloroform were combined to give a 95:5 molar ratio of DSPC/DSPE-PEG2000 or a 55:45 molar ratio of DSPC/Cholesterol, with trace amounts of .sup.14C-cholesteryl hexadecyl ether (.sup.14C-CHE). The resulting mixtures were dried under a stream of nitrogen gas and placed in a vacuum pump overnight. The samples were hydrated at 70.degree. C. with either 300 mM citrate, pH 4.0 (about 600 milliosmoles/kg (mOsm/kg)) or 150 mM citrate buffer, pH 4.0 (about 300 mOsm/kg) and passed through an extrusion apparatus (Northern Lipids Inc., Vancouver, BC) ten times with two 100 nm pore size polycarbonate filters at 70.degree. C. Average liposome size was determined by quasi-elastic light scattering using a NICOMP 370 submicron particle sizer operating at a wavelength of 632.8 nm. The resulting liposomes were applied to a Sephadex G50 column equilibrated with HBS (20 mM HEPES, 150 mM NaCl, about 320 mOsm/kg), pH 7.45 to exchange the external liposomal buffer. Liposomes were subsequently combined with vincristine (and trace amounts of radiolabeled vincristine) at a 0.1:1 drug to lipid weight ratio. To facilitate drug loading, the mixtures were first incubated at 37.degree. C. for ten minutes.

Detail Description Paragraph:

[0086] FIG. 1 shows that retention of vincristine in low-cholesterol liposomes is

significantly enhanced when citrate at an osmolarity of 300 mOsm/kg (150 mM; open circles) is utilized as the internal loading buffer compared to 600 mOsm/kg (300 mM; closed circles). Retention of vincristine in cholesterol containing liposomes is independent of the osmolarity of the intraliposomal solution.

Detail Description Paragraph:

[0087] To further investigate the effect of internal osmolarity on drug retention in low-cholesterol liposomes, daunorubicin was also loaded into DSPC/DSPE-PEG2000 liposomes comprising citrate of either high or low osmolarity. The in vivo retention of daunorubicin was also determined in DSPC/Cholesterol and DSPC/Cholesterol/DSPE-PEG2000 liposomes prepared with an internal citrate concentration of low osmolarity.

Detail Description Paragraph:

[0088] DSPC/DSPE-PEG2000 liposomes (95:5 mole ratio) containing 150 or 300 mM citrate (300 or 600 mOsm/kg), pH 4 and DSPC/Cholesterol (55:45 mole ratio) and DSPC/Cholesterol/DSPE-PEG2000 (50:45:5 mole ratio) liposomes containing 150 mM citrate, pH 4 were prepared as described in Example 1. Liposomes were subsequently combined with daunorubicin at a 0.2:1 drug to lipid mole ratio. To facilitate drug loading, the mixtures were incubated at 40.degree. C. for 60 minutes.

Detail Description Paragraph:

[0090] FIG. 2 shows that, like vincristine (FIG. 1), low-cholesterol liposomes prepared with citrate at 600 mOsm/kg (300 mM; open triangles) as the internal buffer displayed compromised daunorubicin retention in relation to low-cholesterol liposomes with an internal buffer osmolarity of 300 mOsm/kg (150 mM; closed triangles). All values are reported as the mean.+-.SD.

Detail Description Paragraph:

[0091] In order to examine the effect of decreasing internal osmolarity on drug retention in low-cholesterol liposomes, daunorubicin and idarubicin were loaded into DSPC/DSPE-PEG2000 liposomes containing varying amounts of citrate.

Detail Description Paragraph:

[0092] DSPC/DSPE-PEG2000 (95:5 mole ratio) liposomes containing the non-exchangeable marker .sup.3H-CHE were prepared as described in Example 1, except that lipid films were hydrated with 100, 150, 200, 250 or 300 mM citrate, pH 4.0 (corresponding to osmolarity levels of about 200, 300, 400, 500 or 600 mOsm/kg, respectively).

Detail Description Paragraph:

[0095] DSPC/DSPE-PEG2000 (95:5 mole ratio) liposomes prepared with 100, 150 and 300 mM citrate were also loaded with idarubicin at a drug to lipid mole ratio of 0.25:1. Loading was facilitated by incubating the drug and liposomes at 37.degree. C. for 60 minutes. Liposomes were administered to Balb/c mice as indicated and blood samples were removed by cardiac puncture at 0.5, 1, 2, 4 and 24-hours post administration (3 mice per time point). Idarubicin concentration was quantitated using fluorescence intensity at 485 nm as the excitation wavelength and 535 nm as an emission wavelength and using an absorbance wavelength of 482 nm.

Detail Description Paragraph:

[0096] FIG. 3B illustrates that liposomes prepared in the absence of cholesterol and having an internal osmolarity of greater than 500 mOsm/kg (300 mM citrate; closed circles) displayed significantly decreased idarubicin retention in relation to cholesterol-free liposomes with intraliposomal osmolarities of less than 500 mOsm/kg (100 and 150 mM).

Detail Description Paragraph:

[0098] DSPC/DSPG/Chol (70:20:10 mole ratio) were prepared following the methods of Example 1 except that lipid films were hydrated in either saline or Cu(II)

gluconate, pH 7.4 containing 25 mg/mL FUDR at 70.degree. C. Cu(II)gluconate was added at either 100 or 200 mM (321 and 676 mOsm/kg, respectively) and the pH was adjusted to 7.4 by addition of triethanolamine (TEA). Trace amounts of .sup.14C-CHE and .sup.3H-FUDR were used as lipid and drug markers, respectively. The resulting MLVs were extruded at 75.degree. C. through two stacked 100 nm pore size filters for a total of ten passes. Liposomes were buffer exchanged into HBS, pH 7.4 using a hand-held tangential flow column. A total lipid dose of 3.3 .mu.moles (165 .mu.moles/kg) was administered to female Balb/c mice in a final volume of 200 .mu.L immediately after preparation (within 1-2 hrs). Blood samples were removed by cardiac puncture 1, 4 and 24-hours post administration (3 mice per time point). Lipid and FUDR levels were determined using liquid scintillation counting and values were reported as the mean.+-.SD.

Detail Description Table CWU:

1TABLE I Solution mOsm/kg or mOsm/L* 300 mM citrate, pH 4 540 300 mM MnSO.sub.4, 30 mM HEPES, pH 4.7 349 300 mM sucrose, 30 mM HEPES, pH 7.5 380 300 mM MnSO.sub.4, pH 3.5 319 120 mM (NH.sub.4).sub.2SO.sub.4, pH 5.5 276 300 mM sucrose, 20 mM HEPES, 15 mM EDTA, 517 pH.7.5 300 mM citrate, pH 7.5 adjusted with NaHCO3 675 *Units may be interchanged between mOsm/kg or mOsm/L as aqueous solutions were employed

CLAIMS:

7. The composition of claim 1 wherein said intraliposomal aqueous medium comprises citrate.

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L19: Entry 85 of 120

File: USPT

Oct 5, 1999

DOCUMENT-IDENTIFIER: US 5962015 A

TITLE: Stabilized liposomes

Brief Summary Text (8):

Accordingly, there have been many proposals for stabilizing liposomes. Known stabilizers for liposomes include certain relatively simple amphoteric molecules having a cationic region, for example triethanolamine, a common cosmetic buffer, can be added to phospholipid starting materials during liposome preparation to prevent aggregation. Though providing some stability, triethanolamine and the like, do not provide adequate shelf-life and processing stability to enable liposomes to protect actives in a wide range of cosmetic and pharmaceutical formulations.

Detailed Description Text (59):citric acid: 4% glycolic acid 20%[Previous Doc](#)[Next Doc](#)[Go to Doc#](#)